

Allergic Contact Dermatitis from Octisalate and *cis*-3-Hexenyl Salicylate

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A 62-year-old woman developed allergic contact dermatitis from sunscreens containing octisalate (octyl salicylate, 2-ethylhexyl salicylate) and from a fragrance containing *cis*-3-hexenyl salicylate. Results of patch testing and provocative use testing confirmed that she was allergic to octisalate. Provocative use testing indicated that she was also allergic to *cis*-3-hexenyl salicylate.

OCTISALATE (also known as octyl salicylate, ethylhexyl salicylate, and 2-ethylhexyl salicylate [CAS 118-60-5]) is used both as an ultraviolet light absorber and as a fragrance ingredient. The author could find only one previously reported patient with allergic contact dermatitis from this chemical.¹ This was in a large study examining the causes of allergic cheilitis. One of 146 patients had a positive patch-test reaction to octisalate tested at a 5% concentration in petrolatum (R. Strauss, personal communication, January 2004), and this reaction was felt to be clinically relevant.¹ The report of that study focuses on other more common causes of cheilitis and does not discuss the octisalate finding or provide any information about the affected patient.

There is one previous case report of allergic contact dermatitis from *cis*-3-hexenyl salicylate (CAS 65405-77-8).²

Case Report

A 62-year-old white woman described having experienced recurrent severe dermatitis on sun-exposed skin. She always wore sunscreens before being exposed to sunlight. She also had a history of contact dermatitis from some fragrances, fragranced products, and jewelry. She did not have dermatitis at the time of her examination, but dermatitis had been observed by the referring dermatologist.

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Patch testing was performed on the patient's back with standard polypropylene Chemotechnique IQ Chambers (Chemotechnique Diagnostics, Vellinge, Sweden). Test materials included the North American Contact Dermatitis Group standard series,³ eight of the sunscreens sold by Chemotechnique Diagnostics, the patient's most recent sunscreen lotion, numerous fragrance-related allergens, and five commercial fragrances (Tables 1 and 2). The commercial fragrances were applied to 9 × 9 mm IQ Chambers with filter paper inserts and allowed to evaporate for 5 minutes before being applied to the patient.⁴ Patch tests were occluded for 48 hours and delayed readings were performed as noted in Tables 1 and 2. The scoring system was that of the International Contact Dermatitis Research Group (maximum of +++).⁵ Positive patch-test reactions (see Tables 1 and 2) occurred with nickel sulfate 2.5% petrolatum (pet), balsam of Peru (*Myroxylon pereirae*) 25% pet, Cacharel Anaïs Anaïs Eau de Toilette (L'Oréal USA, New York, NY), octisalate 5% pet, and Coppertone Sport Ultra Sweatproof Sunblock SPF 15 (Schering-Plough Health-Care, Kenilworth, NJ). Patch-test results for 35 contact dermatitis patients with the same batch of octisalate 5% pet occluded for 48 hours and read at 48 and 96 hours were negative.

Photopatch testing and minimum erythema dose (MED) testing for ultraviolet A (UVA) were simultaneously performed. The UVA MED was greater than 10 J/cm². The patch tests were removed after 48 hours of occlusion, and one set of the sunscreens was exposed to 10 J/cm² of UVA light. The results were the same as those seen in the sunscreens not exposed to UVA (see Table 1).

A double-blinded right-versus-left antecubital provocative use test (repeat open application test) was performed with octisalate 5% pet versus plain petrolatum. After 4 days

Table 1. Results of Sunscreen Patch Tests

<i>Ingredient or Product</i>	<i>2 Days</i>	<i>4 Days</i>	<i>7 Days</i>
Oxybenzone 10% pet	0	0	0
Octinoxate (ethylhexyl methoxycinnamate) 10% pet	0	0	0
Homosalate 5% pet	0	0	0
Octisalate 5% pet	0	+	+
Octyldimethyl PABA 10% pet	0	0	0
Benzophenone-4 10% pet	0	0	0
Avobenzone 10% pet	0	0	0
Ensulizole (phenylbenzimidazole-5-sulfonic acid) 10% pet	0	0	0
Coppertone Sport Ultra Sweatproof Sunblock SPF 15*	0	+	+

pet = petrolatum; PABA = para-aminobenzoic acid.

*Active ingredients: octisalate 5%, oxybenzone, and octinoxate.

of twice-daily applications, the patient developed contact dermatitis only at the octisalate application site.

The patient declined subsequent patch testing with other salicylates. However, she agreed to a double-blinded right-versus-left antecubital provocative use test with plain petrolatum versus *cis*-3-hexenyl salicylate 3% pet (obtained undiluted from International Flavors and Fragrances, New York, NY). The latter was chosen because it is present in

Cacharel Anaïs Anaïs Eau de Toilette, which caused a positive patch-test reaction (see “Discussion,” below). After 3 days of twice-daily applications, the patient developed contact dermatitis only at the *cis*-3-hexenyl salicylate application site. The result of a 2-week provocative use test with the same preparation on the author’s antecubital skin was negative. Results of patch tests with the same material occluded for 48 hours on 20 control patients were negative at 48 and 96 hours. The patient had no further dermatitis after 1 year of follow-up while using fragrance-free and octisalate-free skin care products.

Discussion

The octisalate concentration in our patient’s sunscreen was 5%, the maximum concentration permitted in the United States.⁶ Allergic contact dermatitis from octisalate was demonstrated by positive patch-test results with octisalate 5% pet, negative patch-test results in 35 control patients, and positive results of double-blinded provocative use tests with octisalate 5% pet.

Our patient had a history of allergic contact dermatitis from various fragrances in addition to sunscreens. This was confirmed by her positive patch-test results with balsam of Peru and Cacharel Anaïs Anaïs Eau de Toilette. However, her positive patch-test reaction to balsam of Peru is probably not explained by an allergy to salicylates because studies of balsam of Peru have not shown salicylates to be present.^{7,8}

At least 13 salicylates are used in fragrances; *cis*-3-hexenyl salicylate is widely used, but octisalate is much less commonly used (Table 3).⁹ The manufacturer indicated

Table 2. Results of Fragrance-Related Patch Tests

<i>Ingredient or Product</i>	<i>2 Days</i>	<i>4 Days</i>	<i>7 Days</i>
Fragrance mix 8% pet	0	0	0
Balsam of Peru 25% pet	+	+	+
Components of fragrance mix 1–2% pet*	0	0	0
Ylang ylang oil 2% pet	0	0	0
Sandalwood oil 2% pet	0	0	0
Menthol 2% pet	0	0	0
Benzyl alcohol 1% pet	0	0	0
Jasmine absolute 2% pet	0	0	0
Vanillin 10% pet	0	0	0
Cacharel Anaïs Anaïs Eau de Toilette	0	+	+
Calvin Klein cK One Eau de Toilette (Phillips-Van Heusen, New York, NY)	0	0	0
Poème Eau de Toilette (Lancôme, New York, NY)	0	0	0
Vanilla Eau de Toilette (Crabtree & Evelyn, Woodstock, CT)	0	0	0
Shalimar Eau de Toilette (Guerlain, Paris, France)	0	0	0

pet = petrolatum.

*Seven components, tested individually.

Table 3. Salicylates in Fragrance Products

<i>Salicylate</i>	<i>Metric Tons Worldwide (2000)</i>
Benzyl salicylate	> 1,000
Hexyl salicylate	> 1,000
<i>cis</i> -3-Hexenyl salicylate	> 100
Isoamyl salicylate	> 100
Methyl salicylate	> 100
Pentyl salicylate	> 100
Phenethyl salicylate	> 10
Ethyl salicylate	> 1
Isobutyl salicylate	> 1
3-Methyl-2-butenyl salicylate	> 0.1
Phenyl salicylate	< 0.1
p-Cresyl salicylate	< 0.01
Ethylhexyl salicylate	< 0.01

Adapted from International Fragrance Association (IFRA).⁹

that the only salicylate in Cacharel Anaïs Anaïs Eau de Toilette is *cis*-3-hexenyl salicylate (Linda Barton, Consumer Affairs Coordinator, L'Oreal USA, personal communication, March 29, 2004). The percentage concentration of *cis*-3-hexenyl salicylate and the identities of other ingredients were not disclosed. However, the maximum average skin level of *cis*-3-hexenyl salicylate in fine fragrances has been reported to be 2%, assuming the use of the fragrance oil at levels of up to 20% in the final product.¹⁰ The results of a double-blinded antecubital provocative use test with *cis*-3-hexenyl salicylate 3% pet was positive whereas the result of a 2-week trial on the author's antecubital fossa was negative. Consistent with a nonirritant explanation for the patient's reaction, this concentration and vehicle did not cause irritation or sensitization in maximization tests on the volar forearms of 25 volunteers.^{11,12}

Cross-reactivity between octisalate and *cis*-3-hexenyl salicylate is not surprising given their similar structures (Fig 1). The only other salicylate included in our patch test series was homosalate (homomenthyl salicylate 5% pet), which gave a negative result. This salicylate has a very different structure (see Fig 1). The degree of cross-reactivity among salicylates is unknown because few reports contain this information. However, the other patient who was reported to be allergic to *cis*-3-hexenyl salicylate was not allergic to hexyl, methyl, phenyl, or benzyl salicylate.²

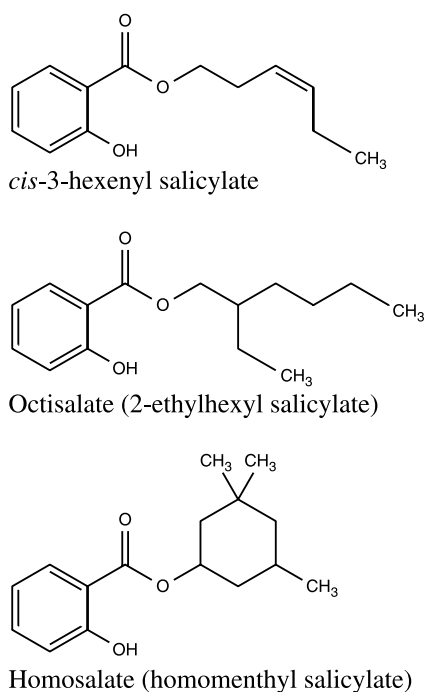


Figure 1. Structure of Tested Salicylates.

Reported cases of allergic contact dermatitis (ACD) from other salicylate esters are rare. These include phenyl salicylate used as an ultraviolet absorber in plastic spectacle frames,^{13,14} lip salves,^{15–17} and a galenic skin cream.¹⁸ Homomenthyl salicylate in a sunscreen lotion caused follicular contact dermatitis in two patients.¹⁹ Positive results from benzyl salicylate patch tests were interpreted as allergic in 3 to 5% of 167 subjects with suspected fragrance allergy.²⁰ Finally, salicylate esters have caused ACD in their use as topical analgesics. These esters include hydroxyethyl salicylate,^{21,22} methyl salicylate,^{23,24} methyl butetisalicylate (also known as diethylacetylsalicylate),²⁵ and 3-(aminomethyl)pyridyl salicylate (also known as picolinamine salicylate).^{26–28} In one case, oral ingestion of acetylsalicylic acid (aspirin) caused recall dermatitis at the site of previous methyl salicylate contact dermatitis.²³ In contrast, our patient frequently ingested aspirin without any adverse reaction, as did several of the patients described above.^{21,25,28}

Summary

We describe a patient with allergic contact dermatitis (ACD) from octisalate in sunscreens and from *cis*-3-hexenyl salicylate in a fragrance product. ACD from octisalate was confirmed both by patch testing and provocative use testing. ACD from *cis*-3-hexenyl salicylate was studied only with provocative use testing.

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